FACTSHEET

NIEHS/NTP SUPPORTS UNIQUE GRANTS PROGRAM

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National Toxicology Program

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The NIEHS Division of Extramural Research and Training (DERT) in collaboration with the National Toxicology Program (NTP) has initiated a new and unique grants program which funds investigator-initiated research to provide data to aid in defining the mechanism of action of agents under study by the NTP. This new program uses the NIH R03 Small Grant mechanism to encourage investigator-initiated hypothesis-driven investigations that utilize animals/tissues/cells from animals undergoing the NTP 2-year cancer bioassay or shorter toxicological characterizations. Applications are requested by a specific Request for Applications (RFA) with specific application deadlines and research objectives. Funding is for 1 or 2 years at $50.000 direct costs per year.

The use of this new program benefits both the NTP and the extramural scientific community. Data provided by the grantees will enable the NTP to expand its expertise base to the scientific community and thereby obtain mechanistic data that cannot be produced in the contract laboratory setting. The scientific community, by taking advantage of the NTP protocols, will have access to animals and tissues they could not afford to generate and will be provided funding to run mechanistic studies in their areas of expertise. The data generated will not only be valuable to the NTP in assessing the mechanism of the toxicity of the tested chemicals but will also provide preliminary data to the investigators that may be useful in generating further independent funding.

Background

The NTP studies a wide variety of environmental, industrial and consumer products for their toxic effects using a broad array of test systems, for the purpose of generating data to strengthen the scientific foundations for risk assessment. These bioassays, which typically employ rats and mice dosed for periods of up to 2 years, are conducted for the NTP in contract laboratories that are proficient in carrying out in-life animal studies. While some "special studies" can be done in contract laboratories to address issues related to mechanism of action, it was recognized that other investigators might take advantage of tissues and other study materials to address research ideas that they may have related to the chemicals under study. It was anticipated that these investigator-initiated research projects, when combined with the wide range of standard data collected, would complement the NTP studies and provide additional mechanistic information to improve the risk assessment process and better protect the public health.

The first small grant Request for Applications (RFA) "Cancer and TEFs for Dioxin and Dioxin-like Chemicals" was released in April 1997 in conjunction with a planned series of 7- 2-yr. cancer bioassays with dioxin and dioxin-like chemicals including several polychlorinated biphenols (PCBs). The purpose was to determine the carcinogenicity of these compounds and to determine the relationship between their carcinogenic potency and their toxic potency as established by their Toxic Equivalency Factor (TEF). The TEF compares the toxicity of each compound relative to that of dioxin (TCDD). The RFA listed numerous possibilities for adjunct investigator-initiated projects including examining the relationship between changes in tissue receptor levels and time, dose and TEF of chemical and establishing the relationship between changes in the activity of cell cycle regulatory proteins with time, chemical and TEF. Investigators could also propose to examine other toxicity

endpoints such as immunotoxicity or reproductive toxicity and to compare the sensitivity of these endpoints to the TEF for the cancer endpoints. Four applications were funded and the investigators worked with NTP staff to develop the research protocols that could be accommodated by the NTP contract laboratories. The grantees were funded to examine the ability of TCDD and the congeners tested to stimulate oxidative stress in the liver and to compare oxidative stress with the TEFs, to examine the role of oxygen free radicals via cytochrome P450 catalyzed oxidative metabolism and its relation to the TEFs, the relation of the stimulation of cytochrome P450s by TCDD and the congeners tested and their TEFs for carcinogenicity and the effects of TCDD and the congeners tested to alter growth factor levels in the intestine and their TEFs.

The second small grant RFA, "Peroxisome Proliferators and Mechanisms of Carcinogenesis" was released in 1998 to encourage investigator-initiated applications to complement the NTP studies on peroxisome proliferators. There is an association between peroxisome proliferators and liver cancer that is of unclear relevance to humans. To help define the mechanism(s) whereby peroxisome proliferators induce cancer in rodents, the NTP designed and carried out 14-, 28-, and 90- day studies with four peroxisome proliferators in male rats, mice and hamsters (non responder). The NTP studies measured numerous endpoints in order to identify a variety of biochemical processes altered by peroxisome proliferators that could be linked to their carcinogenicity. The purpose of the RFA was to generate additional endpoints related to the rodent carcinogenicity of the peroxisome proliferators. Six applications were funded to examine the role of oxidative stress, reactive oxygen species, and protein and gene expression changes in the carinogenicity of these chemicals.

The third small grant RFA "Carcinogenicity of Drinking Water Disinfection By-products" was released in the summer of 1999. The NTP in collaboration with the US EPA is conducting short-term and long-term toxicity studies of four disinfection by-products in order to provide data on which to base predicted safe levels in drinking water. The investigator-initiated studies supported by this RFA will provide additional information on the mechanism of the toxicity/carcinogenicity of these chemicals. The RFA requested studies to determine the relationship between the formation of DNA adducts and carcinogenicity of these chemicals, the relationship between gene expression in the liver and carcinogenicity, and the relationship between exposure to these disinfection by products and oxidative damage, DNA repair and carcinogenicity. Four applications were approved for funding for two years.

Future Grant Opportunities

The NIEHS Division of Extramural Research and Training plans to continue to develop this small grants program in collaboration with the NTP. Areas under discussion for possible future initiatives include the use of investigator-initiated studies to generate data from NTP studies using genomic, proteomic, metabonomic and transgenic technologies. New RFAs, when released, will be found on the NIEHS web page http://www.niehs.nih.gov/ under Grants and Contracts and under the National Toxicology Program web page
http://ntp-server.niehs.nih.gov.

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